PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	01.12.2004
Applicant's or agent's file reference 03/116PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/09746	01.09.2003	30.08.2002

Applicant
VITAK BV et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the International preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Senkel, H Tel. +49 89 2399-8071

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 03/116PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/09746	International filing date *(day/month/year)* 01.09.2003	Priority date *(day/month/year)* 30.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/122		
Applicant VITAK BV et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.03.2004	01.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Zimmer, B Telephone No. +49 89 2399-8600

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/09746

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-15 as originally filed

Claims, Numbers

1-15 filed with telefax on 26.07.2004

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 15 with respect to industrial applicability

   because:

   ☒ the said international application, or the said claims Nos. 15 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,4,6-9,11-13
	No:	Claims	1,2,5,10,14,15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 15 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D4: MH BEERS: "The Merck Manual of Diagnosis and Therapy" 1999, MERCK RESEARCH LABORATORIES , WHITEHOUSE STATION , XP002260508
   D5: EP-A-0 613 877 (EISAI KAGAKU KK) 7 September 1994 (1994-09-07)
   D6: EP-A-1 153 548 (UNILEVER PLC ;UNILEVER NV (NL)) 14 November 2001 (2001-11-14)
   D7: GB-A-2 180 747 (KREITZMAN STEPHEN NEIL) 8 April 1987 (1987-04-08)
   D9: VERMEER C ET AL: 'Role of K vitamins in the regulation of tissue calcification.' JOURNAL OF BONE AND MINERAL METABOLISM. JAPAN 2001, vol. 19, no. 4, 2001, pages 201-206, XP001153227 ISSN: 0914-8779

   The present examination was carried out under the assumption that the priority was validly claimed; therefore, the document WO 03/ 013420 cited as a P-document in the International Search Report was not taken into account for the subsequent examination.

2. Novelty (Art. 33(2) PCT)

2.1 According to the description the subject-matter of the present application encompasses the treatment and prevention of cardiovascular disease conditions including hypertension, left ventricular hypertrophy, congestive heart failure, myocardial

infarction, stroke, Mönckeberg's sclerosis and coronary heart disease (p. 3, l. 6-8).

Prior art document D5 discloses the treatment of ischemic heart diseases such as congestive heart failure with vitamin K derivatives (p. 2, l. 5-8) and the use of menaquinone for promoting bone health, cardiovascular health and prevention of osteoporosis from D6 (claims 14, 15).

Thus D5 and D6 are novelty destroying for the subject-matter of claims 1, 2, 5 and 15 of the present application.

2.2 Prior art document D7 discloses the therapeutic use of a composition comprising vitamin K, vitamin D3, calcium, magnesium and zinc (ex. 4).
As claims 10-14 of the present application are worded as first medical use claims, D7 is novelty destroying for the subject-matter of claims 10 and 14 of the present application.

3. Inventive Step (Art. 33(3) PCT)

3.1 Inventive step cannot be assessed when the requirements of novelty are not met. However, in the light of the above cited prior art, it appears that the problem underlying the present patent application lies in the provision of a new therapeutic use of vitamin K or a derivative thereof. The claimed subject-matter relates, in the light of the above cited prior art to an obvious solution of the problem.

Furthermore, it is known from D9 that calcification of the vessel wall is a process regulated by similar proteins and processes as those known from bone metabolism. As the therapeutic use of vitamin K for the treatment of osteoporosis is known from D6 (see above) the use of vitamin K for the treatment of age related stiffening of arteries and decrease in compliance of arteries according to independent claim 1 of the present application, which are diseases based on calcification of vessel walls (see D4: p. 1658, right col., para. 5) is obvious and does not involve an inventive step.

3.2 Dependent claims 3, 4, 6-9 and 11-13 do not appear to contain any additional features which involve an inventive step when combined with the subject-matter of any claim to which they refer. Dependent claims are only allowable when related to a patentable independent claim (Rule 6.4 PCT).

4. Further remarks

Claim 8 is not supported by the description as required by Art. 6 PCT; according to the description (p. 6, l. 18) the treatment period is 6, 18 and 36 months (Art. 6 PCT).

5. For the assessment of the present claim 15 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Proposed New Claims

(26-07-2004)

1. Use of a composition comprising vitamin K or a derivative thereof, optionally together with vitamin D or a derivative thereof, in the manufacture of a medicament or nutritional formulation for treating or preventing age-related stiffening of arteries, not associated with arteriosclerosis.

2. Use of a composition according to claim 1, wherein said vitamin K is vitamin K_1 (phylloquinone) or vitamin K_2 (menaquinone).

3. Use of a composition according to claim 2 wherein said vitamin K is vitamin K_1 (phylloquinone).

4. Use of a composition according to any one of claims 1 to 3 wherein the daily dosage of vitamin K or a derivative thereof is in the range 50μg-1000μg.

5. Use of a composition according to any one of claims 1 to 4 wherein the medicament or nutritional composition comprises vitamin D or a derivative thereof.

6. Use of a composition according to claim 5 wherein said vitamin D is vitamin D_3 (cholecalciferol).

7. Use of a composition according to any of claims 1 to 6 wherein the medicament or nutritional formulation is for administration to a postmenopausal woman.

8. Use of a composition according to any of claims 1 to 7 wherein the medicament or nutritional formulation is to be administered over a period of at least 12 months, preferably at least 36 months.

9. Use of a composition according to claim 1 wherein said arteries are the common carotid arteries.

10. Use of a composition according to any one of claims 1-9 for promoting healthy arteries, comprising vitamin K or a derivative thereof, optionally together with

vitamin D or a derivative thereof, further comprising one or more additional components selected from: polyphenols, vitamin C, vitamin E (tocopherols and/or tocotrienols), L-arginine, phytosterols, antihypertensive peptides, soluble fibers (e.g. guar, pectin), omega-3, omega-6 and/or omega-9 fatty acids, carnitine, taurine, coenzyme Q10, creatine, folic acid, folates, magnesium, potassium, vitamin B6, and vitamin B12.

11. Use of a composition according to claim 10 which comprises in a single dose: 0.5-1mg vitamin K and 5-10μg vitamin D.

12. Use of a composition according to claim 10 which comprises: 0.5-1.5mg vitamin K; 5-10μg vitamin D; 450-550mg Calcium; 7-12 mg Zinc; and 100-200mg Magnesium.

13. Use of a composition according to claim 12 which comprises about 1mg Vitamin K_1; 8 μg vitamin D_3, 500mg Calcium, 10mg Zinc; and 150mg Magnesium.

14. Use of a composition according to any of claims 10 to 13 which is a food or beverage product or a dietary supplement.

15. A method of preventing or treating age-related arterial stiffening, not associated with arteriosclerosis, comprising administering to a person in need of such treatment an effective amount of vitamin K or a derivative thereof and optionally vitamin D or a derivative thereof.